hESC as tools to investigate the neural crest origin of Ewing's sarcoma

Grant Award Details

hESC as tools to investigate the neural crest origin of Ewing's sarcoma

Grant Type: SEED Grant

Grant Number: RS1-00249

Investigator:

Name:	Elizabeth Lawlor
Institution:	Children's Hospital of Los Angeles
Type:	PI

Disease Focus: Cancer, Pediatrics, Solid Tumors

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $595,576

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: hESC as tools to investigate the neural crest origin of Ewing's sarcoma

Public Abstract:

Human embryonic stem cells (hESC) hold great promise as sources of tissue for regenerative medicine and therapeutics. In addition, their utility as tools to study the origins and biology of human disease must not be underestimated. hESC give rise to tissue-specific adult stem cells and, ultimately, to all mature tissues in the body. As such, disruptions to normal stem cell function can have catastrophic consequences and result in life-threatening or debilitating disease. Understanding how such diseases arise will afford novel insights into how we can better prevent and treat them. Laboratory based studies with hESC therefore stand to make extraordinary contributions to human health.

Human tumors, and in particular the cancers that affect children, often look like tissues that have not developed normally and whose growth has gone unchecked. In fact, recent studies have shown that, in many cases, tumors arise because genetic mutations in the DNA of normal stem cells lead to disordered development, resulting in formation of malignant rather than normal tissues. For example, leukemia can arise when a mutation occurs in a normal blood stem cell, thus inducing formation of cancerous rather than normal blood. Analogous situations exist in other human tissues and their respective tumors. However, because of the relative rarity of normal stem cells in other parts of the body and our inability to effectively isolate them, very little is yet known about how these stem cells go awry and create cancer. hESC, therefore, represent an invaluable resource for the generation of tissue-specific stem cells and for studies of the genesis of human, and in particular, pediatric cancer.

Several different human cancers are believed to arise either directly or indirectly from stem cells called neural crest stem cells (NCSC). NCSC exist in small numbers throughout the body and contribute to the formation of multiple different tissues including the peripheral nervous system and the pigment cells of our skin. It is our central hypothesis that NCSC-derived tumors arise because genetic mutations in NCSC lead to disordered tissue development and the initiation of cancer.

Ewing's sarcoma family tumors (ESFT) are highly aggressive tumors that primarily affect children and young adults. ESFT have a specific mutation in their DNA and this mutation leads to the creation of a cancer-causing gene. We believe that expression of this abnormal gene in NCSC disrupts normal stem cell differentiation and development and, ultimately, leads to ESFT formation. In this proposal we will use hESC as tools to prove or disprove this theory.

Unfortunately, despite highly toxic and aggressive treatment, the survival rate for patients diagnosed with ESFT remains poor. By creating novel hESC-based models to study the origin and biology of ESFT we aim to gain novel insights into the origin and biology of these tumors that will aid in the development of more effective, less toxic therapies.

Statement of Benefit to California:

Human embryonic stem cells (hESC) represent a tremendous resource as tools to study numerous human diseases, including cancer. Cancer claims the lives of over 50,000 Californians, including over 300 children, annually. Laboratory based studies using hESC, such as those proposed in this application, stand to make extraordinary and unique contributions to our understanding of the origin and biology of human cancer. These contributions will ultimately aid in the development of novel therapeutic strategies designed to improve survival and quality of life of cancer patients.

In this proposal we will exploit the power of hESC to study the cellular origins of sarcomas. Sarcomas arise in the bones and soft tissues and primarily affect children and young adults. Despite intensive therapy, the survival rate of patients diagnosed with sarcoma remains poor. The proposed research will provide much needed insight into sarcoma biology and will enable development of novel sarcoma-targeted therapies. In addition, the hESC-derived models that we establish will be readily adaptable to and available for studies of other human cancers.

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